Skeletal Radiology
https://doi.org/10.1007/s00256-020-03511-y

REVIEW ARTICLE

Bone health of transgender adults: what the radiologist needs to know

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Received: 24 April 2020 / Revised: 30 May 2020 / Accepted: 7 June 2020
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Abstract

Sex steroids are important regulators of bone development before puberty and of bone homeostasis throughout adulthood. Gender-affirming therapies with sex steroids are used in transgender and gender diverse persons for treatment of gender dysphoria, which may have profound impacts on their bone metabolism. Many studies have described variable changes in bone density and geometry in transgender cohorts. In order to provide informed guidance on the effect of gender-affirming therapy, the International Society of Clinical Densitometry issued official position statements in 2019 for the performance and interpretation of dual-energy x-ray absorptiometry in transgender and gender-diverse patients. We review the effects of gender-affirming hormone therapy on bone physiology and the changes in bone modulation that have been reported in the literature in transgender patients who have received gender-affirming therapy. We also summarize the recent guidelines for interpretation of dual energy x-ray absorptiometry as an update for the radiologist.

Keywords Gender-affirming hormone therapy · Transgender · Bone mineral density · Quantitative CT · Dual energy x-ray absorptiometry (DXA)

Introduction

Transgender and gender diverse (TGD) persons experience gender incongruence wherein their *gender identity* (inner sense of masculinity, femininity, or other in relation to their environment) is not aligned with their *sex* (male, female, or intersex) assigned to them at birth, which is typically determined by external genitalia or chromosomal analysis. The prevalence of TGD persons varies across studies and countries with general increases in reported prevalence over time [1–4]. An estimated 0.3 to 0.6% of adults in the United States (1.0 to 1.4 million persons) identify as TGD [2, 5, 6]. Transgender women are persons who identify as women and were assigned male at birth and comprise an estimated 5.8 per 100,000 persons worldwide [7]. Transgender men are those who identify as men and were assigned female at birth and comprise an estimated 2.5 per 100,000 persons worldwide [7]. Gender diverse persons are those who do not have a binary gender identity (woman or man) and may be described as nonbinary, gender nonconforming, gender queer, gender fluid, or even bigender. The worldwide prevalence of gender diverse persons is not well known as most studies have not systematically collected demographic data specific to this subpopulation. In our review, we use terms transfeminine (TF) and transmasculine (TF) to describe the directionality of one's gender identity along a spectrum of femininity and masculinity and to be more inclusive of gender diverse individuals. It is important to emphasize that gender identity and sexual orientation are not equivalent, and that gay, lesbian, and bisexual persons may have any gender identity.

According to the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders, persons who suffer psychological or social distress as a result of gender incongruence may be diagnosed with and receive treatments for gender dysphoria [8]. Treatments can include gender-affirming hormone therapy (GAHT) and surgery, which provide relief of dysphoria and improve quality of life [9, 10]. GAHT may

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Published online: 13 June 2020

include feminizing hormones (estrogen, progesterone) for TF persons and masculinizing hormones (testosterone) for TM individuals. Surgical treatment often includes gonadectomy which greatly reduces endogenous sex steroids and necessitates long-term if not lifelong treatment with GAHT.

Sex steroids are critical regulators of bone physiology, and thus, GAHT may have important effects on bone structure in TGD persons. Bone health can be analyzed using dual-energy x-ray absorptiometry (DXA) and quantitative computed tomography (qCT). DXA is a commonly used imaging technique for assessing areal bone mineral density (aBMD) by measurement of photon attenuation of bone derived from a two-dimensional projection. Body composition parameters such as percentages of body fat and lean muscle mass can be derived in the same manner. QCT can assess volumetric BMD (vBMD) and other geometric bone parameters, including differentiation between cortical and trabecular bone [11].

We review the effects of GAHT on bone physiology and the changes in BMD and bone geometry that have been described in both TM and TF groups receiving GAHT. We also provide a summary of the recent ISCD Position Statements for Performance and Interpretation of DXA as an update for the radiologist.

Physiologic effects of GAHT on bone

Sex steroids are important in bone development during puberty and in bone homeostasis during adulthood. Postmenopausal hypoestrogenic states are associated with accelerated bone loss from increased osteoclastic activity in genotypic females [12]. Genotypic males have overall higher BMD than genotypic females, including higher proportions of cortical bone, which may be due to androgen influence. In genotypic males, testosterone supports periosteal bone deposition, while estrogen inhibits periosteal bone formation and promotes endosteal apposition [12]. Hypogonadal males exhibit lower BMD and higher fracture risk, but the association with testosterone levels is unclear. Previous studies have theorized that this lower BMD may be more strongly correlated to circulating estrogen and sex-hormone binding globulin [12, 13].

The influence of GAHT alone on bone physiology in transgender people is not well understood. No differential effect on BMD has been found between the various pharmacological preparations, route of administration, or the time period between initiation of GAHT and gonadectomy [14, 15]. Insufficient hormone replacement after gonadectomy is a known risk factor for low bone density. Other risk factors for low bone density in transgender people include tobacco and alcohol use, low calcium and vitamin D levels, and infrequent weight-bearing activity [12]. Additionally, increased prevalence of metabolic syndrome in TM and TF persons receiving GAHT has been reported [16]. While the relationship of metabolic syndrome with bone density and fracture risk has been established, none of these studies have been performed in a TGD population. Furthermore, despite significant changes in BMI and body composition observed in both TM and TF individuals receiving GAHT, no consistent correlation has been discovered linking these parameters to changes in BMD [14, 17].

Serum measures of bone turnover and hormone status

The effects of GAHT on bone metabolism and BMD have been demonstrated across several studies. Changes in serum concentrations of markers of bone formation (e.g., alkaline phosphatase, osteocalcin, procollagen 1 aminoterminal propeptide) and bone resorption (urinary calcium, hydroxyproline, type 1 collagen C-terminal telopeptide) have been associated with GAHT in both TF and TM persons [14, 18–20]. While measurement of these specific parameters is not part of standard monitoring of treatment in practice, they support a physiologic mechanism for observed BMD changes. Rather, recommended standard clinical monitoring includes measurement of serum levels of estrogen, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) [21], which are more reliable indicators of treatment adequacy and have also been associated with BMD changes.

Transfeminine

Some investigators have shown an inverse correlation between LH and FSH with aBMD in the lumbar spine and hip in TF persons receiving GAHT [14, 22, 23]. However, another study by Weipjes et al. found no association between LH and testosterone levels with changes in BMD due to treatment with anti-androgens. Instead, Wiepjes et al. found that low estradiol (E2) levels were associated with decreases in lumbar spine BMD [24]. The authors therefore postulated that E2 levels may be useful indicators of adequate GAHT dosing.

Transmasculine

Although testosterone does have effects on bone physiology, higher serum testosterone concentrations have not been shown to directly correlate with increases in BMD [24]. Unlike for TF persons, E2 levels were not associated with changes in BMD in TM persons. Both LH and FSH have been inversely correlated with lumbar spine BMD in TM persons across several studies, justifying their use as indicators of the adequacy of therapy and to detect potential non-adherence to masculinizing GAHT [14, 22–24].

Bone mineral density in transfeminine persons

Estrogen is a known modulator of bone metabolism in both men and women exhibiting positive effects on BMD through inhibition of osteoclast function and slowing of bone resorption [12]. Genotypic males produce endogenous estrogen through aromatization of testosterone via the action of aromatase [13]. TF persons who receive antiandrogen therapies or who undergo orchiectomy disrupt estrogen production and in turn alter BMD.

Baseline

Several investigators have described lower bone mass and smaller bone sizes in TF persons prior to the onset of GAHT and orchiectomy, which were closer to measurements of genotypic females [17, 18, 24, 25] (Table 1, Fig. 1). Van Caenegem et al. detected low bone density in 16% of 25 TF subjects (median age 30 years) prior to initiation of feminizing GAHT compared with 4% of male controls [25]. Another study found that BMD at the lumbar spine, hip, femoral neck, and forearm were significantly lower among TF persons compared with genotypic males, with low bone density in 18% of GAHT-naïve TF persons compared with 4% of control males [18]. Similarly, a large study of 711 GAHT-naïve TF persons from the Netherlands found low bone density in 14.2% and low bone mass in 21.9% with average lumbar spine T-scores and Z-scores of − 1.07 ± 1.27 and − 0.93 ± 1.32 (referenced to genotypic males), respectively [24].

Lifestyle factors (physical activity, smoking, diet) have been suggested as possible explanations for the lower baseline BMD measurements. Specifically, TF persons may be less physically active than their genotypic male peers, resulting in less mechanical stresses on the bone [11, 25]. Across several studies, significantly higher smoking rates (range 23.5–43.5%) were observed among TF persons compared with genotypic male controls (17.4% in one study) [11, 15, 24, 29]. Also, vitamin D deficiency was more prevalent among TF persons compared with control males (67–72% vs 32–35%, $p = 0.001$ to 0.01) at baseline [18, 25]. Greater increases in BMD were observed in TF persons who received vitamin D supplementation compared with those who did not during the first year of GAHT [15].

Short-term studies (< 2 years)

Most studies have shown maintenance of aBMD [14, 17, 34] or increase of aBMD [23, 26, 27, 31–33] in TF persons after GAHT and gonadectomy (Table 1, Fig. 1). From the European Network for Investigation of Gender Incongruence (ENIGI) study, a cohort of 231 TF persons from the Netherlands and Belgium, it was shown that BMD increased in the lumbar spine, total hip, and femoral neck within the first year of feminizing GAHT [15]. However, one study demonstrated early (< 24 months) decreases in femoral aBMD after beginning feminizing GAHT, which reversed to levels higher than baseline beyond the first 2 years of treatment out to 59 months [26]. Administration of gonadotropin-releasing hormone (GnRH) analogs in addition to feminizing GAHT resulted in faster decreases in LH in the first 12 months, without negative effects on BMD [35].

Long-term studies (> 2 years)

In general, BMD is preserved among TF persons who continue on consistent GAHT long-term, even among those who undergo orchiectomy (Table 1, Fig. 1). A cross-sectional analysis by Ruetsche et al. showed maintenance of aBMD in TF persons despite antiandrogen therapy, which was considered reflective of preservation of the peak bone mass that subjects had achieved at puberty [23]. Similar findings were found among 46 TF subjects who were followed out to 40 months after GAHT initiation [36]. Ten-year follow-up of 102 TF persons from the Netherlands cohort showed a significant increase in lumbar spine Z-score (+ 0.22 g/cm^2, CI + 0.12 to + 0.32 g/cm^2) with the most increase (+ 0.044 g/cm^2, CI + 0.025 to + 0.063 g/cm^2) among those who were within the highest third for serum estradiol, while those in the lowest third for estradiol had decreased lumbar spine BMD (− 0.036 g/cm^2, CI − 0.044 to − 0.009 g/cm^2) [24]. The same group later demonstrated higher lumbar spine trabecular bone scores (measures of gray-level pixels at DXA to determine trabecular microarchitecture) among TF persons receiving GAHT than those who did not, supporting the idea that trabecular bone is positively influenced by estrogen [37]. Only two studies have demonstrated negative effects of long-term feminizing GAHT on aBMD, with one cross-sectional study showing lower Z-scores at the lumbar spine, hip, and distal radius among 23 TF persons compared with control males.

Prevalence of low bone density and low bone mass[1]

Low bone density and low bone mass are prevalent findings in studies of TF cohorts, especially given that most have included subjects aged 20–40 years. In a study of 50 TF persons after orchiectomy and 3 years of GAHT, the prevalence of low bone mass (Z-score <− 2.0) in the lumbar spine, femoral neck, and hip was 26%, 10%, and 2%, respectively [28]. Dobrolinska and colleagues found 11/61 (18%) of subjects (age 44 ± 11 years) to have low bone density while 5% had

[1] Previous studies in TGD persons have used the term osteoporosis to indicate low bone density in their study populations [10–13, 16, 17, 25, 34]. However, the ISCD 2019 Position Statement reserves the term osteoporosis for all TGD persons over the age of 50 with a T-score of <2.5 [37]. Therefore, we use the phrase "low bone density" in place of osteoporosis for this review.

Table 1 Summary of literature for bone changes in transfeminine persons after gender-affirming therapies as assessed with dual-energy x-ray absorptiometry (DXA)

Publication (year)	Country	Sample size	GAHT exposure	Gonadectomy	Interval	Site	Outcome (aBMD)
Cross-sectional studies							
Reutrakul et al. (1998) [26]	Thailand	28	EE, TE, Ex	No	Group 1: less than 24 months (avg 13.8 months) Group 2: greater than 24 months (avg 58.8 months)	LS, FN, TC	Group 1: NC at any site Group 2: ↑ at all sites Group 2 had higher aBMD compared with group 1
Sosa et al. (2003) [27]	Spain	27	EE + CA, Ex	No	3–35 years	LS, FN	↑ LS and FN aBMD ↑ T-scores and Z-scores at LS and FN (vs. genotypic males)
Ruetsche, Kneubuehl, Birkhaeuser, and Lippuner (2005) [23]	Switzerland	24	EE + CA, then Ex after surgery	Yes	12.5 years	LS, WB, H, TIB	↑ T and WB Z-score (vs. genotypic males)
Lapauw et al. Bone (2008) [11]	Belgium	23	EE, TE, Ex	Yes	4–20 years	LS, H, DR	↓ LS, H, DR aBMD (vs. genotypic males)
T'Sjoen et al. (2009) [28]	Belgium	50	EE + CA, TE + CA, Ex + CA	Yes	Post-surgery 1–26 years. (avg 5 years) Post GAHT 3–33 years. (avg 7.6 years)	LS, WB, H, FN, DR	↓ LS, H, FN aBMD
Wierckx et al. (2012) [29]	Belgium	50	EE, TE, Ex	Yes	Post-surgery 6 months to 32 years. (avg 10 years)	LS, H, DR	↓ aBMD (vs genotypic males)
Miyajima, Kim, and Oda (2012) [30]	Japan	18	Ex (10)	Variable Yes (10) No (8)	Post-surgery 13.2 ± 7.0 months Hormone therapy 32.4 ± 11.2 months	LS	↑ aBMD
Van Caenegem et al. (2013) [25]	Belgium	25	None	No	N/A	LS, H, WB, FN	↓ aBMD at all sites (vs. genotypic males)
Dobrolińska et al. (2019) [22]	Netherlands	68	EE, TE + CA	Yes	83.5 (66.5–111.5) months	LS, H	NC LS aBMD; ↓ H aBMD after 15 years. GAHT and gonadectomy
Follow-up studies							
Van Kesteren et al. (1996) [31]	Netherlands	56	EE + CA, TE + CA, Ex + CA, Cx	No	Baseline, 12 months	LS	↑ aBMD
Van Kesteren, Lips, Gooren, Asscheman, and Megens (1998) [14]	Netherlands	20	Pre-surgery EE + CA Post-surgery EE, TE, Ex	Yes	Baseline, 12 months, 28–63 months	LS	↑ aBMD (12 months) then ↓ to baseline
Mueller et al. (2005) [32]	Germany	40	Ex + Cx	No	Baseline, 12, 24 months	LS, FN	↑ aBMD at LS (12 months+) and FN (24 months) ↑ Z-score at LS and FN
Dittrich et al. (2005) [33]	Germany	60	Ex + Cx	No	Baseline, 12 months, 24 months	LS, FN	Increased aBMD at LS and FN at 12 months (not statistically significant). ↑ LS aBMD at 24 months.
Haraldsen, Haug, Falch, Egeland, and Opjordsmoen (2008) [17]	Norway	12	EE	No	Baseline, 3 months, 12 months	LS, TIB, FN	↓ aBMD (vs genotypic males) at baseline and 12 months
Mueller et al. (2011) [34]	Germany	84	Ex + Cx	No	Baseline, 12 months, 24 months	LS, FN	↑ LS aBMD NC FN aBMD
Van Caenegem et al. (2015) [18]	Belgium	49	EE, TE	No	Baseline, 12 months 24 months	LS, WB,	↓ aBMD and Zg at baseline at all sites.

Table 1 (continued)

Publication (year)	Country	Sample size	GAHT exposure	Gonadectomy	Interval	Site	Outcome (aBMD)
						H, FN, R	Increased aBMD at LS, WB, FN, R with follow-up but did not reach statistical significance.
Gava et al. (2016) [35]	Italy	40	CA (20) Cx + TE	No	Baseline, 12 months	LS, WB	NC with either therapy after 12 months
Wiepjes et al. (2017) [15]	Netherland, Belgium	231	EE + CA TE + CA	No	Baseline, 12 months	LS, H, FN	↑ aBMD at all sites
Fighera, da Silva, Dal-Ri Lindenau, and Spritzer (2018) [36]	Brazil	142	CA or Cx + Ex or TE	Variable	Baseline, 3 months, 12 months Subset of 46 patients followed 12–40 months (avg 31 months)	LS, FN, TF,	aBMD similar to genotypic female control at all sites. ↓ aBMD and Zg at all sites. No change of aBMD in longer follow-up subset
Wiepjes et al. (2019) [24]	Netherlands	711	EE, TE, CA	Variable	Baseline, repeated every 2–5 years. while on GAHT, compared at 10 years	LS, H, FN	↓ baseline aBMD at LS ↑ aBMD for highest tertile of estradiol and ↓ aBMD for lowest tertile of estradiol ↑ Zg NC at H and FN

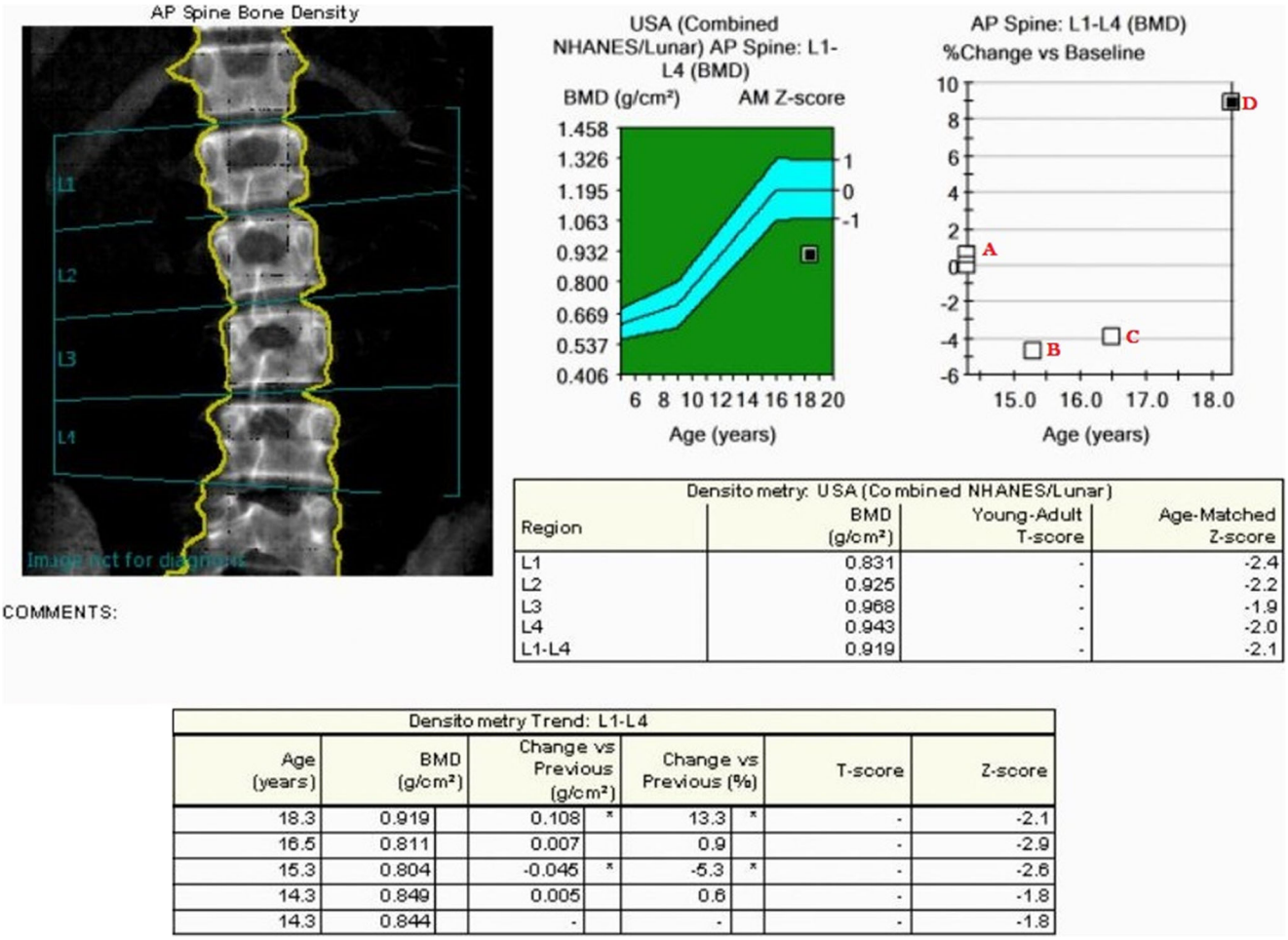
GAHT gender-affirming hormone therapy, *EE* oral ethinyl estradiol, *TE* transdermal estradiol, *Ex* estrogen preparation other than ethinyl estradiol, *CA* cyproterone acetate, *Cx* antiandrogen other than CA, *aBMD* areal bone mineral density (g/cm^3), *LS* lumbar spine, *FN* femoral neck, *H* hip, *TF* total femur, *TC* trochanter, *TIB* tibia, *WB* whole body, *DR* distal radius, *Z-score* standard deviation from the mean BMD of age-matched healthy population, *Zg* z-score versus genotypic control, *NC* no difference/no change, ↑ = higher/increased, ↓ = lower/decreased

low bone mass an average of 7 years after start of feminizing GAHT and 5 years after orchiectomy [22]. In Brazil, low bone mass (referenced to genotypic men) was found in 18% of 142 TF persons (age 33.7 ± 10.3), who had received GAHT for at least 3 months, and was strongly correlated with lean mass [36]. Another study noted low bone density in 23.4% of TF persons by lumbar spine measurements and in 25.5% by distal radius measurements, despite maintenance of feminizing GAHT an average of 9 years across the cohort [29]. In a cross-sectional study of BMD among 24 TF persons, Ruetsche et al. noted five subjects who developed low bone density (referenced to genotypic males). These subjects were later determined to be non-adherent to their prescribed GAHT regimens based on serum analyses that showed low levels of estradiol and elevated FSH [23].

Bone mineral density in transmasculine persons

Masculinizing GAHT seems to prevent bone loss from estrogen deficiency in TM persons, even among those who undergo oophorectomy (Table 2). The ability of TM persons to maintain BMD during GAHT is either a direct effect of testosterone on bone, indirect effects of peripheral aromatization of testosterone to estradiol, or greater mechanical loading associated with androgen-mediated increases in muscle mass [20, 29, 39]. Several studies have demonstrated maintenance of BMD at sites with a higher relative proportion of trabecular bone (lumbar spine) and increases at sites containing more cortical bone (femoral neck, hip) [23, 39, 41, 43]. For example, one study demonstrated higher BMD within the tibial diaphysis, epiphysis, and whole body among TM persons and maintenance of BMD at the hip compared with age-matched female controls [23]. The authors attributed these findings to androgen stimulation in areas of relatively higher concentrations of cortical bone found in the distal tibia.

In theory, the hypoestrogenic state associated with masculinizing GAHT might be expected to cause a loss of BMD, which would be further accelerated after oophorectomy [30, 38]. In fact, measurable decreases in lumbar spine BMD were observed among TM persons over a 2- to 5-year period after undergoing oophorectomy and beginning masculinizing GAHT, which may have been attributable to insufficient GAHT [14]. Another study showed lower average lumbar spine BMD among TM persons whose GAHT included both masculinizing GAHT and oophorectomy, while those only receiving masculinizing GAHT had significant increases in BMD compared with controls [38]. The same study showed that subjects who had oophorectomy and stopped or were inconsistent in taking GAHT experienced a 25% reduction in BMD compared with controls [38].



Densitometry: USA (Combined NHANES/Lunar)			
Region	BMD (g/cm²)	Young-Adult T-score	Age-Matched Z-score
L1	0.831	-	-2.4
L2	0.925	-	-2.2
L3	0.968	-	-1.9
L4	0.943	-	-2.0
L1-L4	0.919	-	-2.1

Densitometry Trend: L1-L4								
Age (years)	BMD (g/cm²)		Change vs Previous (g/cm²)		Change vs Previous (%)		T-score	Z-score
18.3	0.919		0.108	*	13.3	*	-	-2.1
16.5	0.811		0.007		0.9		-	-2.9
15.3	0.804		-0.045	*	-5.3	*	-	-2.6
14.3	0.849		0.005		0.6		-	-1.8
14.3	0.844		-		-		-	-1.8

Fig. 1 Eighteen-year-old transfeminine follow-up lumbar spine DXA (combined NHANES/Lunar female database). Densitometry trend chart (bottom of image) and %change vs. baseline graph in top right of image show baseline lumbar spine BMD at age 14 (**a**) below normal for age which significantly decreased by 5.3% by age 15 (**b**). Gender-affirming hormone therapy (leuprolide-acetate and oral estrogen) initiated at age 15 following point B. Insignificant 0.9% increase in lumbar spine BMD at age 16 (**c**) with significant 13.3% increase on current study at age 18 (**d**). Note that the lumbar spine BMD remains below normal for age when compared with the cis-gender female database

Baseline

Prior to initiation of GAHT, BMD in TM persons has been in line with that reported among genotypic female controls (Table 2). Multiple studies have shown no significant differences in DXA-measured bone parameters between GAHT-naïve TM persons and control females [17, 20, 38, 39], including a recent study of a large cohort of 543 TM persons [24]. A small study of 23 TM persons showed that measures of BMD and bone turnover prior to beginning GAHT were comparable to those of control females, despite higher rates of smoking and lower vitamin D levels in the TM group [20].

Short-term studies (< 2 years)

Most prospective studies have reported no change in lumbar spine BMD within the first year of masculinizing GAHT [17, 38, 41, 42] (Table 2). A prospective study of 23 TM persons showed no significant changes in lumbar spine, femoral neck, and whole aBMD after 12 months, and modest increases at the hip [20]. Another study involving 15 subjects followed over 24 months also showed maintenance of lumbar spine BMD and demonstrated a 7.8% increase in BMD at the femoral neck [41]. A large study by Wiepjes et al. of 199 subjects demonstrated an increase in BMD at both the lumbar spine and total hip after 12 months, which was most pronounced among those aged 50 years and older (post-menopausal), which the authors attributed to peripheral aromatization of testosterone to estradiol [15]. A single retrospective study from Japan found that lumbar spine BMD progressively declined among TM persons after initiation of testosterone and oophorectomy. The investigators suggested that their findings may be related to lack of ovarian aromatase activity and increased bone resorption given concomitant increases in urine type 1 collagen N-telopeptide NTX [30].

Table 2 Summary of literature for bone changes in transmasculine persons after gender-affirming therapies as assessed with dual-energy x-ray absorptiometry (DXA)

Publication (year)	Country	Sample Size	GAHT Exposure	Gonadectomy	Interval	Site	Outcome (aBMD)
Cross-sectional studies							
Goh and Ratnaml (1997) [38]	Singapore	5	PT	None	1–3 years	LS	↑ aBMD (vs. untreated)
		27	PT	Yes	2–12 years	LS	↓ aBMD (vs. untreated) NC (vs age-matched reference)
		32	PT	Yes	0.5–8 years. (inconsistent dosing)	LS	↓ aBMD (vs untreated)
Ruetsche, Kneubuehl, Birkhaeuser, and Lippuner (2005) [23]	Switzerland	15	PT	Yes	8 years	T, W-B	↑ Z-score (vs genotypic controls)
Wierckx et al. (2012) [29]	Belgium	50	PT	Yes (49/50), no (1/50)	10 years	LS, H, DR	NC aBMD at all sites
Van Caenegem (2012) [39]	Belgium	50 16	PT Pre-PT	Yes No	9 months -22 years	LS, H, FN	NC aBMD at all sites
Miyajima, Kim, and Oda (2012) [30]	Japan	50	PT	Yes (32) No (18)	33.4 ± 12.3 months; 18.2 ± 7.8 months	LS	↓ aBMD
Broulik, Urbánek, and Libanský (2018) [40]	Czech Republic	35	PT	Yes	216 ± 36 months	LS, FN	↑ FN aBMD (vs genotypic controls); NC LS aBMD
Dobrolińska et al. (2019) [22]	Netherlands	43	PT	Yes	87 (73–150) months	LS, H	NS LS aBMD; ↓ H aBMD after 15 years GAHT and gonadectomy
Follow-up studies							
Van Kesteren et al. (1996) [31]	Netherlands	35	PT, Tx	No	Baseline and 12 months	LS	NC aBMD
Goh and Ratnaml (1997) [38]	Singapore	10	PT	Yes	6–59 months	LS	NC aBMD
Van Kesteren, Lips, Gooren, Asscheman, and Megens (1998) [14]	Netherlands	19	PT	Yes	Baseline, 12 months, 28–63 months	LS	NC (12 months) then ↓ aBMD
Turner et al. (2004) [41]	United States	15	PT	No	Baseline, 12 months, 24 months	LS, FN	↑ LS aBMD; NC FN aBMD
Haraldsen, Haug, Falch, Egeland, and Opjordsmoen (2008) [17]	Norway	21	PT	No	Baseline, 3 months, 12 months	LS, F-N, W-B	NC aBMD all sites
Mueller et al. (2010) [42]	Germany	45	PT	No	Baseline, 12 months, 24 months	LS, FN	Increased BMD at LS and FN and FN Z-scores but did not reach statistical significance; NC LS Z-scores
Pelusi, et al. (2014) [43]	Italy	45	PT	No	Baseline, 12 months	LS, W-B	NC aBMD
Van Caenegem, et al. (2015) [20]	Belgium	23	PT	No	Baseline, 12 months	LS, F-N, H, W-B, R	NC aBMD all sites

Table 2 (continued)

Publication (year)	Country	Sample Size	GAHT Exposure	Gonadectomy	Interval	Site	Outcome (aBMD)
Wiepjes et al. (2017) [15]	Netherlands, Belgium	199	PT	No	Baseline, 12 months	LS, H, FN	↑ LS, H aBMD; NC FN aBMD
Wiepjes et al. (2019) [24]	Netherlands	543	PT	Yes	Baseline, repeated every 2–5 years, compared at 10 years	LS, H, FN	↑ LS aBMD for ages ≥ 40, highest tertile of estradiol level, lowest tertile of baseline BMD, and lowest tertile of LH concentration NC TH, FN aBMD ↑ LS Zg

GAHT gender-affirming hormone therapy, *PT* parenteral testosterone ester, *Tx* oral testosterone, *aBMD* areal bone mineral density (g/cm^3), *LS* lumbar spine, *FN* femoral neck, *H* hip, *TIB* tibia, *WB* whole body, *DR* distal radius, *Z-score* standard deviation from the mean BMD of age-matched healthy population, *Zg* z-score versus genotypic control, *NC* no difference/no change, ↑ = higher/increased, ↓ = lower/decreased

Long-term studies (> 2 years)

In general, lumbar spine BMD is maintained among TM persons who consistently receive masculinizing GAHT beyond 2 years from initiation [14, 23, 40, 41] (Table 2). Studies have shown maintenance of aBMD at other sites including the hip and distal forearm for those followed for an average of 10 years [29, 39]. Wiepjes et al. recently published 10-year follow-up data from 70 TM persons, which demonstrated a significant increase in lumbar spine BMD in those older than 40 years [24]. In addition, several studies have shown increases in total hip BMD and increases in BMD at other sites composed of greater proportions of cortical bone (tibia, whole body) [23, 40, 41]. Conversely, a single study showed significant decreases in total hip BMD in TM persons after 15 years of GAHT after values reached their highest peak between 10 and 15 years after initiation of GAHT [22]. A similar decrease in total hip BMD was observed 15 years after oophorectomy [22].

Prevalence of low bone density and low bone mass

Low bone density and low bone mass are generally much less prevalent among GAHT-naïve TM persons than has been described in TF persons. Across a cohort of 543 TM persons with median age of 25 years, low bone density was found in only 2.4% and low bone mass in 4.3% at baseline (using female reference values) [24]. Another study of 43 TM persons aged 39 ± 10 years who were an average 7 years after initiation of masculinizing GAHT and 5 years after oophorectomy found low bone density in only 4% and low bone mass in none [22]. A different study found no instances of low bone density among 50 TM subjects followed for an average of 10 years after GAHT and oophorectomy [29].

Quantitative computed tomography in TGD persons

DXA measures change in aBMD by two-dimensional analysis and may not be as accurate in quantification of larger bones of greater depth, misinterpreting them as being denser. However, quantitative CT (qCT) provides a three-dimensional analysis of the bone geometry, allowing precise measurement of cortical and trabecular bone including measures of volumetric BMD (vBMD) and bone size (periosteal and outer cortical circumferences, cortical bone area, and thickness), as well as soft tissues (fat and lean muscle), the latter of which may also affect aBMD at DXA. While qCT may provide a more accurate assessment of bone health, it may not be as readily available as DXA in clinical practices. A summary of the literature regarding qCT analysis in TGD persons is presented in Table 3.

Transfeminine

In a cross-sectional study, Lapauw et al. measured vBMD using pQCT and observed lower trabecular vBMD in the distal radius, overall smaller bone size, and smaller periosteal circumference in TF persons compared with genotypic male controls [11]. However, the subjects were subjected to one full year of androgen deprivation with cyproterone acetate prior to initiation of estrogen, which may have caused a substantial decrease in vBMD from lack of estrogenic support.

Another cross-sectional study of 50 TF subjects who had undergone gonadectomy and who received feminizing GAHT for an average of 7.6 years had lower bone size and lower muscle mass at both the distal radius and tibia compared with control males [28]. Van Caenegem et al. found that GAHT-naïve TF subjects had lower trabecular vBMD, smaller radial and tibial bone sizes, and less muscle mass compared with male controls despite similar body mass indices and smoking

Table 3 Summary of literature for bone changes in transgender persons after gender-affirming therapies as assessed with quantitative computed tomography (qCT)

Publication (year)	Country	Sample Size	GAHT Exposure	Gonadectomy	Interval	Site	Outcome (aBMD)
Cross-sectional studies							
Lapauw et al. Bone (2008) [11]	Belgium	23 TF	EE, TE, Ex	Yes	8 (4–20) years	R, T-IB	↓T-vBMD (R) NC C- vBMD (R, TIB) ↓CBA (R, TIB) ↓PC (R, TIB) ↓EC (R) ↓CorT (TIB)
T'Sjoen et al. (2009) [28]	Belgium	50 TF	EE, TE, Ex	Yes	7.6 (3–33) years	R, T-IB	↓bone size at both sites. (vs genotypic controls)
Van Caenegem (2012) [39]	Belgium	50 TM 16 TM	PT Pre-PT	Yes No	9 months -22 years	LS, F-N	↑T-vBMD (R) ↓C-vBMD (R, TIB) ↑CBA (R) ↑PC (R) ↑EC (R)
Follow-up studies							
Van Caenegem et al. (2015) [18]	Belgium	49 TF	EE + CA TE + CA (>45yo)	No	Baseline, 12 months, 24 months	R, T-IB	*Baseline:* ↓ T-vBMD, CBA (R) ↓ CBA, CorT, PC (TIB) NC all other parameters (R, TIB) *12 or 24 months:* ↑T-vBMD at 24 months (R) NC all other parameters (R, TIB)
Van Caenegem et al. (2015) [20]	Belgium	23 TM	PT	No	Baseline, 12 months	R, T-IB	*Baseline:* NC all parameters (R, TIB) *12 months:* ↑T-vBMD (R) NC all other site parameters

GAHT gender-affirming hormone therapy, *EE* oral ethinyl estradiol, *TE* transdermal estradiol, *Ex* estrogen preparation other than ethinyl estradiol, *CA* cyproterone acetate, *PT* parenteral testosterone ester, *Tx* oral testosterone, *TBA* trabecular bone area, *T-vBMD* trabecular volumetric bone mineral density (mg/cm^3), *C-vBMD* cortical volumetric bone mineral density (mg/cm^3), *CBA* cortical bone area (mm^3), *PC* periosteal circumference (mm), *EC* endosteal circumference (mm), *CorT* cortical thickness (mm), *LS* lumbar spine, *FN* femoral neck, *H* hip, *TIB* tibia, *WB* whole body, *R* radius, *TF* transfeminine persons, *TM* transmasculine persons, *NC* no difference/no change, ↑ = higher/increased, ↓ = lower/decreased

status. Their results corroborate the results of previous aBMD studies [18, 25]. Cortical measurements were unchanged after 2 years of GAHT, while radial trabecular vBMD increased [18].

Transmasculine

Masculinizing GAHT has been positively associated with increases in trabecular vBMD, cortical parameters (cortical bone area, periosteal, and endosteal diameters), and overall bone size at qCT. Gains in distal radial trabecular vBMD were observed after the first 12 months of masculinizing GAHT [20]. Similar findings were also observed after an average of 10 years, at which point gains in cortical bone area and bone size were also demonstrated [20, 39]. The authors proposed that increases in cortical bone and trabecular vBMD may reflect physio-mechanical factors related to androgen-stimulated increases in muscle mass and mechanical loading on bone [20, 39].

ISCD 2019 position statements

A Task Force was convened by the International Society of Clinical Densitometry (ISCD) aimed at answering questions pertaining to use of DXA to monitor bone density in TGD patients. In December 2019, formal position statements were issued after careful review of the available literature on the effects of GAHT on bone metabolism and density changes in TGD populations [44] (Table 4). In keeping with the Endocrine Society guidelines [21], the ISCD and this review support the position that assessment of BMD in TGD persons should only occur when risk factors for low bone density exist. Given the reported high prevalence of low bone density and low bone mass among GAHT-naïve TF persons, a

Table 4 Consensus statements: International Society of Clinical Densitometry 2019 [44]

Position	Indications	Quality of evidence
Position 1: Baseline BMD indicated for TGD persons if they have any of the following:	- History of gonadectomy or therapy that lowers endogenous gonadal steroid levels prior to initiation of hormone therapy - Hypogonadism with no plan to take GAHT - Existing ISCD indications for BMD testing, such as glucocorticoid use and hyperparathyroidism	- Transgender men and women: Good, A, W - Gender non-conforming/non--binary: Poor, C, W
Position 2: Follow-up BMD could be done in TGD persons when the results are likely to influence patient management, such as:	- Low bone density as defined by current ISCD guidelines - Individuals taking pubertal suppressants, such as GnRH analogs - Nonadherence or inadequate doses of GAHT - Plan to discontinue GAHT - Presence of other risks for bone loss or fragility fractures - BMD testing intervals should be individualized based on the patient's clinical status: typically, every 1–2 years until BMD stabilizes or improves, with longer intervals thereafter	- Transgender men and women: Good, B, W - Gender non-conforming/non--binary: Poor, C, W
Position 3: T- and Z-score calculation in TGD individuals	- T-scores should be calculated using a uniform Caucasian (non-race adjusted) female normative database for all transgender individuals of all ethnic groups. Recommend T-score of ≤ − 2.5 for diagnosis of osteoporosis in all TGD persons age 50 years or older, regardless of hormone status.	- Grade: Good, A, W
	- Z-scores should be calculated using the normative database that matches the individual's gender identity	- Transgender women: Good, A, W - Transgender men: Fair, B, W
	- If requested by the ordering provider, Z-scores may also be calculated using the normative database that matches the sex recorded at birth	- Poor, C, W
	- In gender non-conforming/non-binary persons, the normative database that matches the sex recorded at birth should be used	- Poor, C, W
	- Gender data should be obtained on the intake questionnaire	- Poor, C, W
Position 4: Parameters included in the DXA report	- Parameters included in the DXA report for TGD persons are the same as for the general population, but when requested may include Z-scores calculated according to both male and female normative databases	- Poor, C, W
Regarding fracture risk calculations (FRAX)	- There are no meaningful direct data on fracture risk in TGD persons and therefore no scientific basis upon which to recommend which gender to use in calculating fracture risk in TGD persons	- Not reported.

baseline DXA should be considered [44]. In TM subjects, neither baseline nor serial DXA is indicated unless a patient develops risk factors for bone loss, including non-adherence to GAHT [21, 24, 44]. The ISCD recommends that DXA reports include the same parameters that would be reported for the general population and, as for all patients, T-scores of TGD persons should be calculated using non-race adjusted genotypic female references [44].

However, debate exists as to which reference database is best to use in the determination of Z-scores which are usually matched to one's age, race, and sex. In their cross-sectional study of aBMD in 24 TF subjects treated long-term, Ruetsche et al. suggested that feminizing GAHT leads to preservation of BMD [23]. They also found higher genotype-matched Z-scores at sites of relatively higher cortical bone in that cohort, concluding that this may have been a reflection of the existing peak bone mass the subjects had achieved at puberty prior to beginning GAHT. Therefore, using Z-scores matched to genotype may be more beneficial [23]. However, the current literature indicates that GAHT-naïve TF persons tend to have lower BMD than genotypic male controls and that both their BMD and TM BMD are more in line with that of genotypic female controls [24, 36, 45, 46]. This position is supported by a large study by Wiepjes et al. that calculated Z-scores using both male and female references for 711 TF and 543 TM GAHT-naïve subjects and determined that Z-scores of both groups were more closely aligned with genotypic female controls [24]. Of note, other smaller studies have suggested that BMD and Z-scores for TM persons may be more appropriately referenced to genotypic males [17, 23, 40]. Therefore, the Task Force advises that Z-score should be calculated according to the database that matches the patient's *gender identity*,

but radiologists may report Z-scores using the database for the patient's genotypic sex, if desired by the referring provider [44]. For these reasons, it is also recommended for imaging facilities to collect both gender identity and sex recorded at birth on intake forms [44].

Limitations and future study

Fracture risk

Despite the observed changes in BMD and bone geometry in TGD populations, the clinical implications of long-term administration of GAHT and gonadectomy on fracture risk are still unknown. Collectively, the few studies that include data on fracture prevalence prior to initiation of GAHT are composed of 74 TF and 23 TM participants in total. These studies have shown no difference in the number of fractures compared with genotype-matched controls [18, 20, 25]. Short-term follow-up studies out to 2 years found no fractures among 49 TF [18] and 23 TM subjects [20]. The definition of fracture in those studies was variable and may not have always represented true insufficiency fractures. However, one study found no osteoporotic fractures among 53 TF and 53 TM persons who were assessed after the first year of GAHT [47]. Of note, these studied populations have all been relatively young, with ages ranging from 16 to 47 [18, 20, 25, 45, 47].

After publication of the ISCD document, a large retrospective analysis of 2023 TF persons (1089 younger than and 934 older than 50 years) who had been maintained on feminizing hormones for 8 and 19 years, respectively, found a higher risk of fracture among older TF persons compared with age-matched control males (4.4% vs 2.4%, OR 1.90 CI 1.32–2.74) and was similar when compared with age-matched control females (4.2%, OR 1.05, CI 0.75–1.49) [48]. There was also a trend toward a higher fracture risk among younger TF persons compared with age-matched control females (2.4% vs 1.6%, OR 1.49 CI 0.96–2.32) that approached but did not reach statistical significance [48]. Fracture among TM persons was not statistically different than the risk for age-matched referenced females (OR 0.79, CI 0.48–1.30) and was lower than that for age-matched reference males (OR 0.57, CI 0.35–0.94) [48].

Associations were found between fracture risk and lower lumbar spine BMD among TF subjects and lower estradiol levels among TM subjects [48]. Interestingly, the distribution of fractures reported among TF persons showed more frequent involvement of hip, spine, forearm, and humerus, which was comparable to the fracture distribution among reference females rather than reference males. Smoking among TF persons tended to be associated with fracture risk, although this did not reach statistical significance [48]. Therefore, lifestyle factors (physical activity, vitamin D intake, smoking), rather than feminizing GAHT, seem to be significant contributors to low bone density and potentially insufficiency fractures among TF patients, but this relationship requires greater study.

Variation in GAHT regimens and timing of surgery

Considerable variation in GAHT regimens exists across the literature including hormone preparations and doses, route of administration, age of initiation, and timing of gonadectomy. Much of the literature did not address BMD changes that may be different between patients who only receive GAHT and those who also undergo gonadectomy which may confound results. Most of these studies were conducted in Europe where cyproterone acetate was almost universally administered as an antiandrogen for TF persons, but that drug is not available in the United States and spironolactone or GnRH agonists are used instead. Therefore, the applicability of these data to worldwide populations is uncertain.

Bone health in gender diverse populations

There are no explicit data which evaluate changes in BMD and fracture risk among gender diverse (nonbinary, nonconforming, gender queer, etc) persons, who may identify outside of a gender binary. These individuals may desire to receive varying degrees of gender-affirming therapies, such as reduced doses of GAHT, or decline to undergo gonadectomy, or no therapy altogether [44, 46]. Given limitations in data for this subgroup, it is currently recommended to reference DXA parameters to the database of their genotypic sex as recorded at birth [44].

Bone health in TGD youth

Recognition and treatment of gender dysphoria among TGD youth have led to an increase in the use of GnRH analogs for pubertal blockade [49]. As these are initiated before children have reached the ages of skeletal maturity, BMD assessment will be further complicated, with potential need to establish new comparison nomograms. Until more is known, it may be advisable to report BMD referenced to both male and female references for persons who received pubertal blockade or GAHT as youth [21, 45, 46, 50].

Conclusion

GAHT has important effects on osseous physiology, but seems to have no deleterious effects on the bone health of TGD people when administered appropriately. TF persons tend to begin with low BMD and small bone size which improve after initiation of GAHT, but these parameters tend to remain lower than those of genotypic male controls.

Conversely, TM persons are typically able to maintain or increase their BMD, potentially from androgen-mediated effects on cortical bone. Emerging data continue to shed light on the utility of DXA for evaluation of BMD among TGD patients with recent issuance of formal recommendations from the ICSD. Additional studies using qCT may provide more granular insight into the effects of GAHT on bone geometry. Large, prospective multicenter studies are needed to determine fracture risk among TF and TM cohorts. Radiologists who are aware of current guidelines as well as uncertainties regarding bone health in TGD patients will be well equipped to advise their clinical colleagues and to provide the most appropriate care for TGD patients.

Authors' contributions Justin T. Stowell, M.D.: conception and design, acquisition of data/literature review, analysis and summary of data into Tables 1, 2, 3, and 4; drafting and revision of article for final approval; accountable for all aspects of the work.

Hillary W. Garner, M.D.: analysis and summary of data into Tables 1, 2, and 3; drafting and revision of article for final approval; accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. Eur Psychiatry. 2015;30(6):807–15.
2. Meerwijk EL, Sevelius JM. Transgender population size in the United States: a meta-regression of population-based probability samples. Am J Public Health. 2017;107(2):e1–8.
3. Gates GJ. How many people are lesbian, gay, bisexual, and transgender? Los Angeles: The Williams Institute; 2011.
4. Wiepjes CM, Nota NM, de Blok CJM, Klaver M, de Vries ALC, Wensing-Kruger SA, et al. The Amsterdam cohort of gender dysphoria study (1972-2015): trends in prevalence, treatment, and regrets. J Sex Med. 2018;15(4):582–90.
5. Flores AR, Herman JL, Gates GJ, Brown TNT. How many adults identifiy as transgender in the United States? The Williams Institute: Los Angeles; 2016.
6. Crissman HP, Berger MB, Graham LF, Dalton VK. Transgender demographics: a household probability sample of US adults, 2014. Am J Public Health. 2017;107(2):213–5.
7. Collin L, Reisner SL, Tangpricha V, Goodman M. Prevalence of transgender depends on the "case" definition: a systematic review. J Sex Med. 2016;13(4):613–26.
8. Association AP. Diagnostic and statistical manual of mental disorders (DSM-5). Fifth ed. Arlington: American Psychiatric Association; 2013.
9. Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet JC, Pringuey D, et al. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. J Nerv Ment Dis. 2013;201(11):996–1000.
10. Papadopulos NA, Zavlin D, Lelle JD, Herschbach P, Henrich G, Kovacs L, et al. Male-to-female sex reassignment surgery using the combined technique leads to increased quality of life in a prospective study. Plast Reconstr Surg. 2017;140(2):286–94.
11. Lapauw B, Taes Y, Simoens S, Van Caenegem E, Weyers S, Goemaere S, et al. Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. Bone. 2008;43(6):1016–21.
12. Cauley JA. Estrogen and bone health in men and women. Steroids. 2015;99(Pt A):11–5.
13. Cawthon PM, Schousboe JT, Harrison SL, Ensrud KE, Black D, Cauley JA, et al. Sex hormones, sex hormone binding globulin, and vertebral fractures in older men. Bone. 2016;84:271–8.
14. van Kesteren P, Lips P, Gooren LJ, Asscheman H, Megens J. Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. Clin Endocrinol. 1998;48(3):347–54.
15. Wiepjes CM, Vlot MC, Klaver M, Nota NM, de Blok CJ, de Jongh RT, et al. Bone mineral density increases in trans persons after 1 year of hormonal treatment: a multicenter prospective observational study. J Bone Miner Res. 2017;32(6):1252–60.
16. Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, et al. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. J Psychosom Res. 2015;78(4):399–406.
17. Haraldsen IR, Haug E, Falch J, Egeland T, Opjordsmoen S. Cross-sex pattern of bone mineral density in early onset gender identity disorder. Horm Behav. 2007;52(3):334–43.
18. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, et al. Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study. Osteoporos Int. 2015;26(1):35–47.
19. Vlot MC, Wiepjes CM, de Jongh RT, T'Sjoen G, Heijboer AC, den Heijer M. Gender-affirming hormone treatment decreases bone turnover in transwomen and older transmen. J Bone Miner Res. 2019;34(10):1862–72.
20. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, et al. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). Eur J Endocrinol. 2015;172(2):163–71.
21. Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102(11):3869–903.
22. Dobrolinska M, van der Tuuk K, Vink P, van den Berg M, Schuringa A, Monroy-Gonzalez AG, et al. Bone mineral density in transgender individuals after gonadectomy and long-term gender-affirming hormonal treatment. J Sex Med. 2019;16(9):1469–77.
23. Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K. Cortical and trabecular bone mineral density in transsexuals after

long-term cross-sex hormonal treatment: a cross-sectional study. Osteoporos Int. 2005;16(7):791–8.
24. Wiepjes CM, de Jongh RT, de Blok CJM, Vlot MC, Lips P, Twisk JWR, et al. Bone safety during the first ten years of gender-affirming hormonal treatment in transwomen and transmen. J Bone Miner Res. 2018;34(3):447–54.
25. Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman JM, et al. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. Bone. 2013;54(1):92–7.
26. Reutrakul S, Ongphiphadhanakul B, Piaseu N, Krittiyawong S, Chanprasertyothin S, Bunnag P, et al. The effects of oestrogen exposure on bone mass in male to female transsexuals. Clin Endocrinol. 1998;49(6):811–4.
27. Sosa M, Jodar E, Arbelo E, Dominguez C, Saavedra P, Torres A, et al. Bone mass, bone turnover, vitamin D, and estrogen receptor gene polymorphisms in male to female transsexuals: effects of estrogenic treatment on bone metabolism of the male. J Clin Densitom. 2003;6(3):297–304.
28. T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, et al. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. J Clin Densitom. 2009;12(3):306–13.
29. Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, et al. Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med. 2012;9(10):2641–51.
30. Miyajima T, Kim YT, Oda H. A study of changes in bone metabolism in cases of gender identity disorder. J Bone Miner Metab. 2012;30(4):468–73.
31. van Kesteren P, Lips P, Deville W, Popp-Snijders C, Asscheman H, Megens J, et al. The-effect of one-year cross-sex hormoneal treatment on bone metabolism and serum insulin-like growth factor-1 in transsexuals. J Clin Endocrinol Metab. 1996;81(6): 2227–32.
32. Mueller A, Dittrich R, Binder H, Kuehnel W, Maltaris T, Hoffmann I, et al. High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. Eur J Endocrinol. 2005;153(1):107–13.
33. Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A. Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonist. Exp Clin Endocrinol Diabetes. 2005;113(10):586–92.
34. Mueller A, Zollver H, Kronawitter D, Oppelt PG, Claassen T, Hoffmann I, et al. Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. Exp Clin Endocrinol Diabetes. 2011;119(2):95–100.
35. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. Clin Endocrinol. 2016;85(2):239–46.
36. Fighera TM, da Silva E, Lindenau JD, Spritzer PM. Impact of cross-sex hormone therapy on bone mineral density and body composition in transwomen. Clin Endocrinol. 2018;88(6):856–62.
37. Wiepjes CM, Vlot MC, de Blok CJM, Nota NM, de Jongh RT, den Heijer M. Bone geometry and trabecular bone score in transgender people before and after short- and long-term hormonal treatment. Bone. 2019;127:280–6.
38. Goh HH, Ratnam SS. Effects of hormone deficiency, androgen therapy and calcium supplementation on bone mineral density in female transsexuals. Maturitas. 1997;26(1):45–52.
39. Van Caenegem E, Wierckx K, Taes Y, Dedecker D, Van de Peer F, Toye K, et al. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. J Clin Endocrinol Metab. 2012;97(7): 2503–11.
40. Broulik PD, Urbanek V, Libansky P. Eighteen-year effect of androgen therapy on bone mineral density in trans(gender) men. Horm Metab Res. 2018;50(2):133–7.
41. Turner A, Chen TC, Barber TW, Malabanan AO, Holick MF, Tangpricha V. Testosterone increases bone mineral density in female-to-male transsexuals: a case series of 15 subjects. Clin Endocrinol. 2004;61(5):560–6.
42. Mueller A, Haeberle L, Zollver H, Claassen T, Kronawitter D, Oppelt PG, et al. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. J Sex Med. 2010;7(9):3190–8.
43. Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. J Sex Med. 2014;11(12): 3002–11.
44. Rosen HN, Hamnvik OR, Jaisamrarn U, Malabanan AO, Safer JD, Tangpricha V, et al. Bone densitometry in transgender and gender non-conforming (TGNC) individuals: 2019 ISCD Official Position. J Clin Densitom. 2019;22(4):544–53.
45. Singh-Ospina N, Maraka S, Rodriguez-Gutierrez R, Davidge-Pitts C, Nippoldt TB, Prokop LJ, et al. Effect of sex steroids on the bone health of transgender individuals: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2017;102(11):3904–13.
46. Davidge-Pitts C, Clarke BL. Transgender bone health. Maturitas. 2019;127:35–42.
47. Wierckx K, Van Caenegem E, Schreiner T, Haraldsen I, Fisher AD, Toye K, et al. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. J Sex Med. 2014;11(8):1999–2011.
48. Wiepjes CM, de Blok CJ, Staphorsius AS, Nota NM, Vlot MC, de Jongh RT, et al. Fracture risk in trans women and trans men using long-term gender-affirming hormonal treatment: a Nationwide cohort study. J Bone Miner Res. 2020;35(1):64–70.
49. Lopez CM, Solomon D, Boulware SD, Christison-Lagay ER. Trends in the use of puberty blockers among transgender children in the United States. J Pediatr Endocrinol Metab. 2018;31(6):665–70.
50. Vlot MC, Klink DT, den Heijer M, Blankenstein MA, Rotteveel J, Heijboer AC. Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone. 2017;95: 11–9.

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Key Points for the Radiologist

Notable changes in bone mineral density and bone geometry are known to occur among transgender and gender diverse people who receive gender-affirming therapies.

Transfeminine persons may have low bone mineral density and small bone size prior to the initiation of gender-affirming therapies. Although feminizing hormones seem to improve bone mineral density initially, long-term data show bone mineral density and cortical size to be lower than that of genotypic male controls. This difference may be a consequence of non-hormonal lifestyle factors.

Transmasculine persons who receive gender-affirming therapies are typically able to maintain or increase their bone mineral density, especially at sites with a higher proportion of cortical bone.

Although gender-affirming therapies are considered safe when administered appropriately, the implications on long-term fracture risks are still unknown.